Mast cells and cancer: enemies or allies?

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Mast cells are a component of cancer microenvironment the role of which is complex and poorly understood. Mast cells promote cancer growth by stimulation of neoangiogenesis, tissue remodeling and by modulation of the host immune response. The mediators of cancer promotion include protease-activated receptors, mitogen activated protein kinases, prostaglandins and histamine. Histamine may induce tumor proliferation and immunosuppression through H1 and H2 receptors, respectively. The mast cell-derived modulators of immune response include also interleukin 10 (IL-10), tumor necrosis factor α (TNF-α) and CD30L. Possibly stimulation of angiogenesis is the most important. Mast cells release potent proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), TNF-α and IL-8, and mast cells' enzymes, like metaloproteinases (MMPs), tryptase and chymase participate in vessels' formation. The anti-cancer actions of mast cells include direct growth inhibition, immunologic stimulation, inhibition of apoptosis and decreased cell mobility; the mediators of these processes include chymase, tryptase, TNF-α, IL-1 and IL-6. The very same mediators may exert both pro- or anti-cancer effects depending on concentration, presence of cofactors or location of secreting cells. In fact, peri- and intra-tumoral mast cells may have dissimilar effects. Understanding of the role of mast cells in cancer could lead to improved prognostication and development of therapeutic methods targeting the mast cells.

Key words: mast cells, cancer, microenvironment, angiogenesis.

Introduction

Virchow already suspected that inflammation and cancer are intimately connected; at that time there were no tools for confirming this view, as well as that of Paget who coined the "seed and soil" theory. Until recently, the cancer study has thus concentrated on analyzing the cancer cells themselves. The bulk of information available is huge and our understanding of the phenomena behind neoplastic transformation is expanding. Only in the 1980s the concept of microenvironment was introduced. Since when, we have become increasingly aware of interactions between the cancer and its environment. The cancer microenvironment includes fibroblasts and myofibroblasts, extracellular matrix, preexistent and newly forming vessels, as well as inflammatory cells. The function of the inflammation may be extremely complex: beside the very obvious immunologic reaction against the cancer cells, the participants of an inflammatory and reparative process are truly necessary for cancer progression. In fact, cancer was regarded as a "non healing wound" [1-3]. While we are able to produce a sketchy picture of the function of lymphoid cells or macrophages, understanding of other participants is scarce or lacking. One of such forgotten cells of cancer-stromal interaction is the mast cell (MC) (Fig. 1).

The MCs may be responsible themselves for this relative negligence. The MCs are usually a minor component of the tissue, and quite difficult to detect. A characteristic feature used for MC detection is the expression of proteinases, such as tryptase and chymase. The expression of chymase gives a further insight as some MCs are more equal than others, in fact some express tryptase only, while others both tryptase and chymase; this may influence their function [3-5].

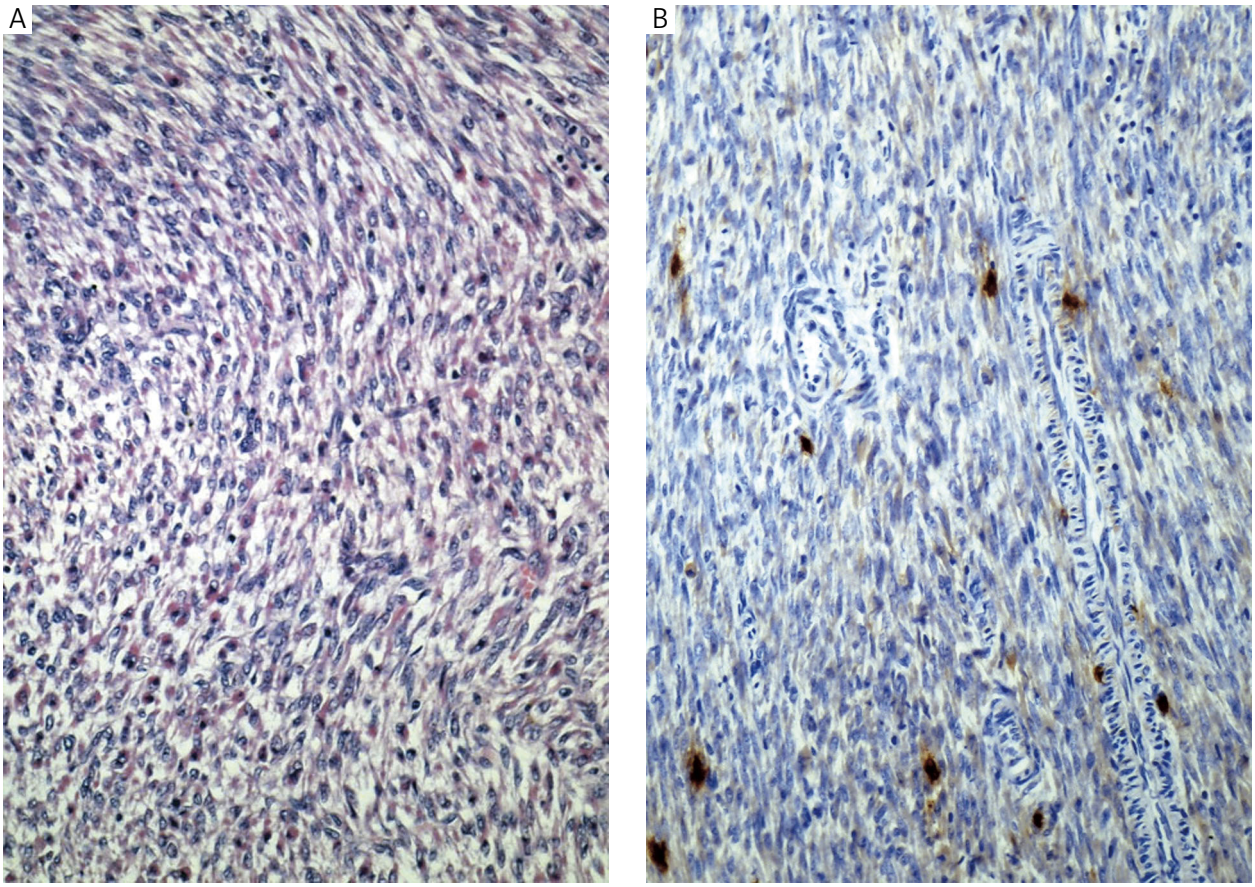

Fig. 1. Mast cells are quite frequently seen as a component of uterine smooth muscle tumors. These cells may interfere with the mitotic count essential for the assessment of the tumor biology. A) HE, magnification 200×, B) immunohistochemistry for tryptase, magnification 200×

The MC is a ubiquitous bone-marrow derived cell, a silent inhabitant of most tissues and organs. Its role becomes important in the very first phases of inflammation and becomes extraordinary in the allergic process. The relationship between inflammation, mast cells and cancer might be quite complicated, featuring both promotion and inhibition of the tumor growth (Fig. 2).

Mast cells as cancer promoters

The cancer stimulating mechanisms operated by MCs include participation in immunosuppression, the release of proangiogenic and mitogenic factors and involvement in the degradation of the extracellular matrix [6].

The MCs may also directly influence growth of the cancer cells [7-11]. Yoshii *et al.* showed that tryptase may be responsible for stimulation of cancer growth, specifically through the protease activated receptor (PAR-2), MAP kinase activation and prostaglandin E2 release.

The best known mast cell product is histamine and it can play a role in tumor progression. Bowrey *et al.* showed that tumor histamine content correlates positively with the mast cell count in breast carcinomas [12]; this suggests that mast cells are indeed the principal source of the tumor histamine. Histamine can induce tumor proliferation through H1 receptors and suppress the immune system through H2 receptors. Both may be involved in human carcinogenesis [13]. The presence of H3 and H4 histamine receptors in human breast carcinoma cells were also described [14]. Activation of H2 receptor by histamine increases cell proliferation in NMU-induced mammary tumor [15]. What is more, Medina *et al.* [14] showed a direct correlation of endogenous histamine levels with malignant behavior of mammary cells. Histamine modulated the proliferation in MDA-MB-231 breast cancer cells in a dose-dependent manner. Histamine also plays a role in the growth-inducing activity of mast cell culture media on thyroid carcinoma cells [16]. Stabilization of mast cells could decrease neurofibroma growth [17]. Mast cells were shown to be required for generation of neurofibromas in neurofibromatosis type 1, both in humans and in animal models [18]. Yoshida *et al.* [19] studied histamine-positive cells and plasma histamine levels in NF1 patients with different types of neurofibromas. In cutaneous neurofibromas and diffuse plexiform neurofibromas there were many histamine-positive cells, though, in nodular plexiform neurofi-

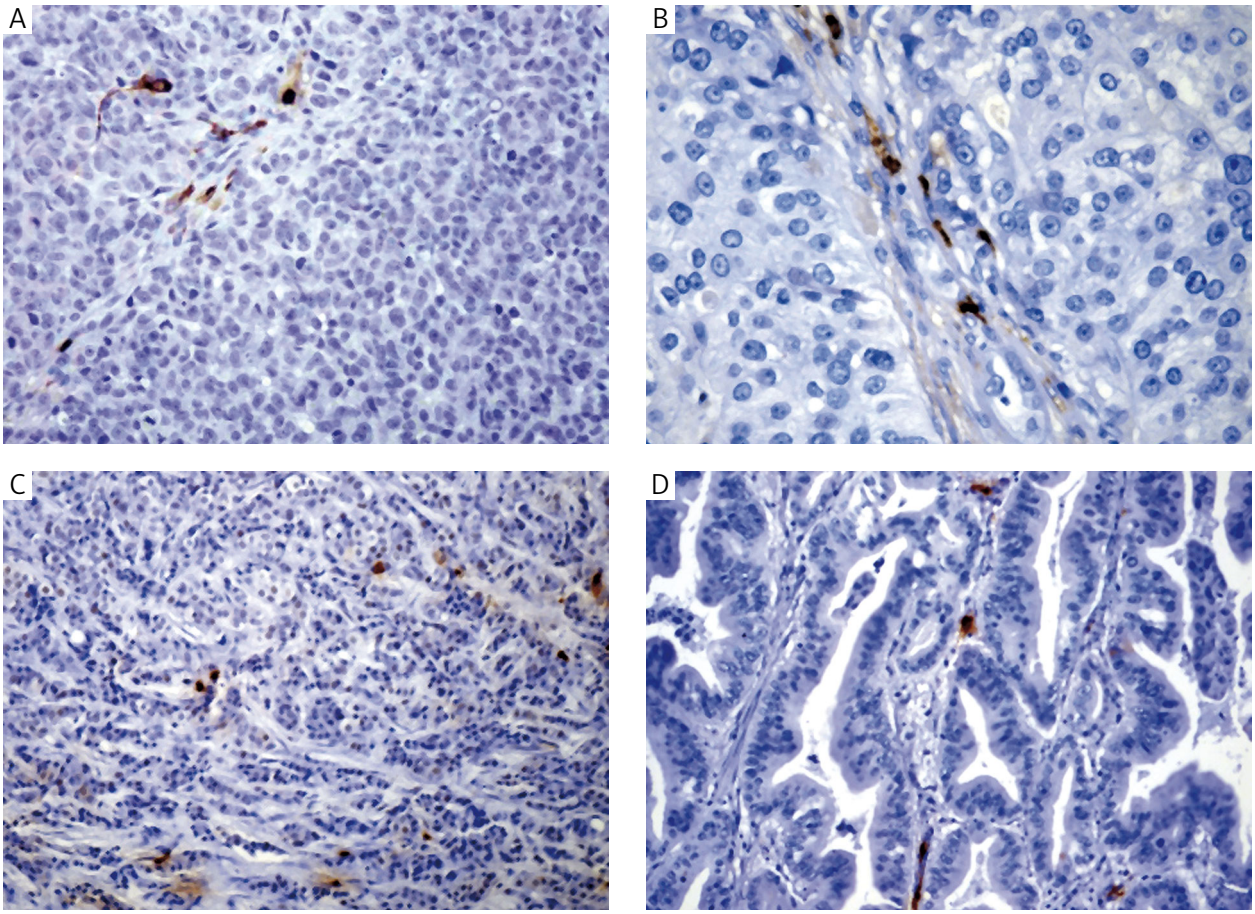

Fig. 2. Tryptase positive cells in the stroma of: malignant melanoma (A); renal urothelial carcinoma (B), breast carcinoma (C), and colorectal adenocarcinoma (D)

bromas there were only a few. It was suggested that the number of histamine-positive cells depends on the size of the tumor and in smaller tumors located superficially, the histamine-positive cell counts might be higher.

Mast cells may also contribute to cancer growth by modulation of the immune response. Secretion of histamine, interleukin 10 (IL-10) and tumor necrosis factor α (TNF-α) leads to suppression of the cellular immunity. Mast cell interaction with regulatory T-cell (T_{reg}) modulates the function of both cell types. T_{reg} inhibits mast cell progenitors and suppresses degranulation of mature mast cells. Mast cells in turn inhibit expression of IL-10 by T_{reg} and promote differentiation of pro-inflammatory ΔT_{reg} [20]. In hepatocellular carcinoma, mast cell count in combination with T_{reg} number could predict the outcome more effectively than the mast cell count alone [21]. In colorectal carcinoma, mast cells may play a critical role to reverse the anti-inflammatory function of the regulatory T-cells [22]. Mast cells also induce CD8+ T cells activation and proliferation; in endometrial carcinoma, tryptase-positive mast cell counts correlate to CD8+ count and these parameters increase with cancer progression [23]. Hart *et al.* [24] suggest that mast cells contribute to the development of basal cell carcinoma by initiating immunosuppression. They claim that a higher number of mast cells in non-sun-exposed skin leads to basal cell carcinoma development. Histamine might also protect against ionizing radiation, with obvious therapeutic implications [25]; on the other hand, MDA-MB-231 breast cancer cells were sensitized to radiation by histamine [14]. There are reports that Hodgkin's lymphoma patients with many mast cells in their tumor tissue have a worse prognosis. Mast cells produce functionally active CD30 ligand (CD30L) and the poorer prognosis has been proposed to be caused by stimulation of Reed-Sternberg cells by CD30L [26]. In a pancreatic β-cell tumor model, activation of Myc *in vivo* triggered rapid recruitment of mast cells to the tumor site. Such a recruitment was necessary for macroscopic tumor expansion [27].

Possibly the most important factor by which mast cells may influence cancer growth is stimulation of angiogenesis. Mast cells seem to stimulate angiogenesis mainly in the early phase of tumor development, while at later stages tumor cells become self-sufficient with regard to production of proangiogenic factors [28]. Secreting mast cells can induce and enhance angiogenesis via multiple interacting pathways. They release

potent proangiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β), TNF-α and IL-8 [29-31]. Tryptase also has proangiogenic action with its ability to degrade connective tissue matrix and ability to activate PAR-2 receptors expressed on endothelial cells [7, 32]. Chymase was also shown to be pro-angiogenic [33]. Mast cells secrete also professional extracellular matrix digesters, such as MMP-2, and they convert pro-MMP-9 (inactive form) into MMP-9 (active form) [28, 34]. Proteinases and heparin released by mast cells stimulate heparin-binding pro-angiogenic factors located on cell surfaces and in the extracellular matrix. Histamine, VEGF, and lipid-derived mediators induce microvascular hyperpermeability. Mast cells recruit macrophages and lymphocytes, activate platelets and other non-mast cells which secrete pro-angiogenic factors. ECM remodeling and changes in microenvironment may in turn change the number, function and phenotype of mast cell population [30]. All of the above-mentioned functions of mast cells may influence cancer progression and metastatic spread.

Mast cells as cancer fighters

The anti-neoplastic actions might include direct inhibition of cell growth, increased inflammatory antitumor reaction, induction of apoptosis and decreased cell mobility. The opposite effects of the same mast cell might depend on its ability to degranulate or secrete specific mediators in response to a variance of stimuli. Tryptase causes tumor cells disruption and chondroitin sulphate may inhibit tumor cells dissemination and metastasis formation [21]. Mast cells might also be able to recruit both M1 and M2 macrophages, which are well known to have opposite effects on tumor growth. Another important factor is the heterogeneity of mast cells, especially the presence of both chymase positive and chymase negative cells; these may differ in their products and also in response to stimuli [35].

Some mediators released by mast cells show an inhibitory effect on tumor growth and angiogenesis, specifically TNF-α, IL-1 and IL-6 have been reported to suppress melanoma growth. Additionally, phenotype and secretory patterns of mast cells can be altered by microenvironmental factors which result in the release of specific mediators. For example, low pH promotes IL-4 and IL-6 production without concomitant histamine release. Some mediators that have well-established proangiogenic functions may paradoxically inhibit progression of the tumor. It is postulated that histamine can increase prostacyclin synthesis by endothelial cells, and prostacyclin is a potent antimetastatic factor [6]. Some studies have shown the direct tumor cytotoxicity of mast cells. Activation of TLR2 on mast cells and subsequent release of IL-6 results in the inhibition of tumor growth both *in vitro* and *in vivo*. Recruitment of NK cells and CD3+ T cells by mast cells has also been observed [36]. In a mouse melanoma model, recruitment of eosinophils by tryptase and promotion of their survival by mast cell derived IL-5 leads to tumor regression [37].

Clinical impact

The clinical significance of tumor-related mast cells remains only partially understood. Among many functions of mast cells promoting tumor growth, their contribution to neoangiogenesis seems to be most important. The participation of mast cells in the progression of cancer and in neoangiogenesis has been shown in several cancer types; specifically pulmonary carcinoma [38], colorectal carcinoma [11, 32], neurofibromas [39], prostatic carcinoma [40-42] and various skin tumors including basal cell carcinoma and melanomas [6, 8, 43]. Ribatti *et al.* measured angiogenesis and microvessel counts in human endometrial carcinoma [44]. The number of microvessels was highly correlated with MC tryptase-positive cell counts, moreover these parameters raised with tumor progression. A similar outcome in the uterine cervix carcinoma [45] and in pulmonary adenocarcinoma [46] was observed.

Carlini *et al.* showed that patients with the non small cell pulmonary carcinoma and a high chymase positive mast cell count inside the tumors had higher vascular density. It has also been shown that the patients with higher peritumoral mast cell count had a higher chance of survival [38]. Mauro *et al.* performed a similar analysis of colorectal carcinoma. They reported a correlation between mast cell counts and vascular density, and a higher survival rate for patients with lower mast cell counts at the tumoral/stromal interface [11]. Ribatti *et al.* [47] found the density of mast cells to parallel microvessel density in progression of gastric carcinoma. This relationship was seen for both chymase and tryptase.

Location (perhaps) matters!

The issue of MCs' clinical impact is further complicated by the existence of both intratumoral and peritumoral mast cells (Fig. 3) with a possibly divergent significance. Most studies suggest that peritumoral mast cells are more numerous than intratumoral; it was also observed that intratumoral mastocytes contain less granules; this might indicate a more extensive secretion [11, 32, 38].

A high intratumoral mast cell count was identified as a good prognostic factor in prostatic cancer by Fleischmann *et al.* [40] and Nonomura *et al.* [42]. It was an independent factor only in the latter study, though. Johansson *et al.* [41] confirmed these results. The same

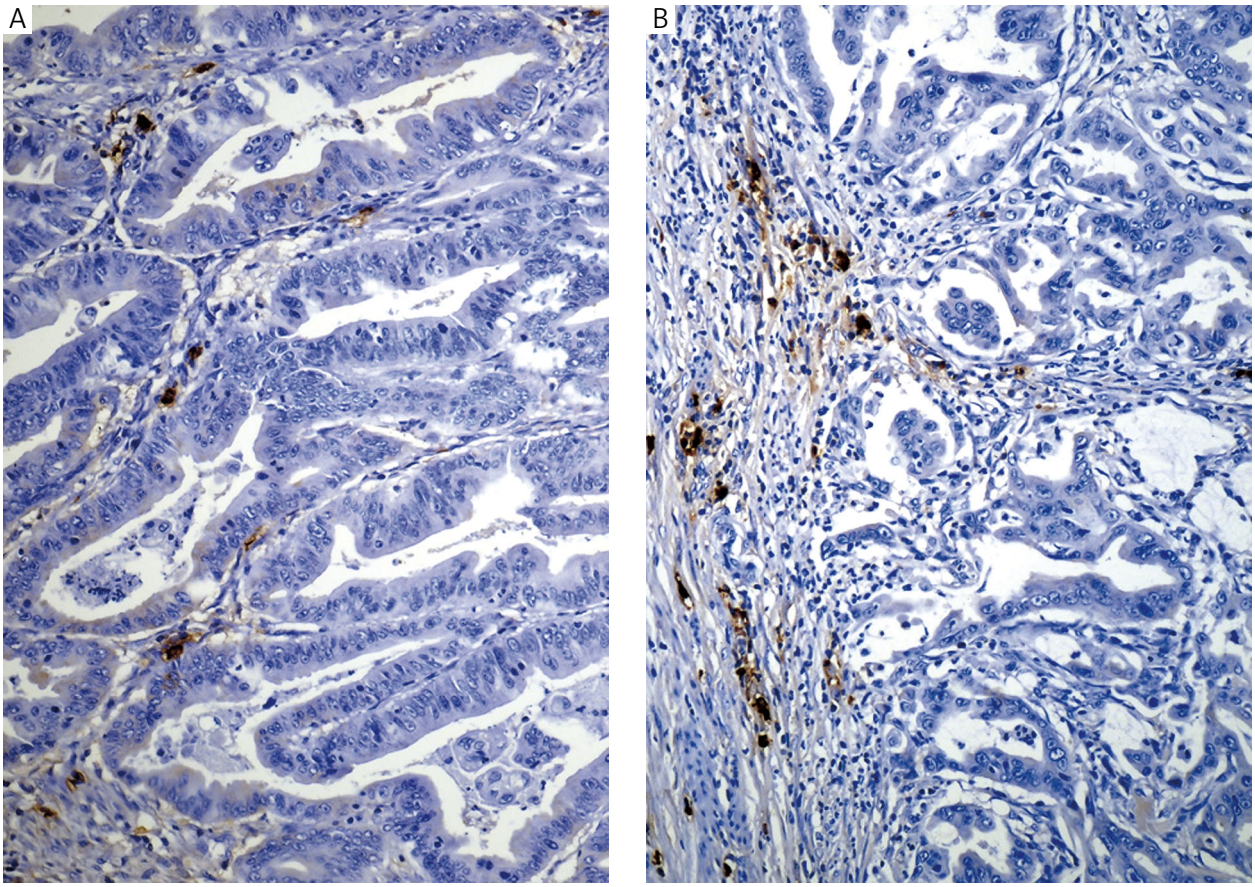

Fig. 3. Tryptase-positive cells in the stroma of colorectal adenocarcinoma (A), and an even higher number of tryptase-positive cells at the tumor interface (B). Immunohistochemistry, magnification 200×

study showed that a patient with a high peritumoral mast cells count fare significantly worse. The two populations of mast cells would thus have opposite effects on survival.

It was postulated that mast cells accumulate around melanomas and promote their growth, specifically by the release of proangiogenic factors. In fact, peritumoral mast cell counts correlate strongly with microvessel density, presence of the metastases and prognosis [9, 31, 48, 49]. Melanoma cells may attract mast cells by producing mast cell chemotactic/mitogenic factors such as IL-3 or FGF-2. The recruitment of mast cells, and subsequent release of heparin, bFGF, histamine, or TNF-α favors tumor progression, featuring a self-perpetuating regulatory loop [48, 50].

In addition to the clinical significance of mast cells, their participation in the process of carcinogenesis is of particular interest; however this topic is not well explored.

Mast cells may promote the growth of cancer cells directly (vide supra). Mast cells have also been shown to regulate proliferation of blood vessels, and to participate in induction of angiogenic switch, necessary for a fully malignant phenotype. Wilk *et al.* [51] have seen a stepwise increase of tryptase-positive and chymase-positive mast cells from normal mucosa, to cervical intraepithelial neoplasia, and ultimately to invasive cervical carcinoma. A similar progression of mast cell numbers was described for oral dysplasia and cancer [52]. In addition, mast cells were also shown to participate in the progression of cutaneous tumors. Our group has suggested a possible role of MCs in progression from melanocytic nevus to melanoma [53].

Possible therapeutic impact

As any important factor in cancer pathogenesis, tumor-associated mast cells may represent a target for treatment. Bowrey *et al.* [12] used cimetidine in breast cancer patients. This compound blocks histamine receptors, but is also known to inhibit activation of mast cells. The study showed only a minimal and non significant effect on tumor growth. As tryptase and chymase are important for cancer progression, inhibition of these proteinases might be promising. Compounds targeting tryptase are underdeveloped, and although designed as anti-allergic, might have an antitumor effect as well [54, 55].

Some of the currently known "targeted" therapeutic methods may target mast cells as well. This may be voluntary or an unexpected effect. The c-kit tyrosine kinase is targeted by imatinib and other com-

pounds. SCF/c-Kit signaling is crucial for mast cells [56]. The former is selectively inhibiting the receptor altered in gastrointestinal stromal tumors, but not the wild form present on mast cells. Other formulations, as antiangiogenic sunitimib, sorafenib or nilotinib may have a broader spectrum of action. What is more, the non-neoplastic cancer-accompanying cells might be less prone to develop mutation-driven resistance. Such antitumor effect mediated by mast cell inhibition was shown in neurofibromas [18], both in the experimental model of neurofibromatosis and in single human subjects.

The net effect on cancer development may be difficult to assess, with unexpected results due to the complexity of regulatory networks.

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